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Updates in Management of Acquired Bone Marrow Failure Conditions

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Consultancy and Honoraria: Novartis; BMS; Daichii- Sankyo; AAMDSIF

Discussion of off-label drug use: Not applicable

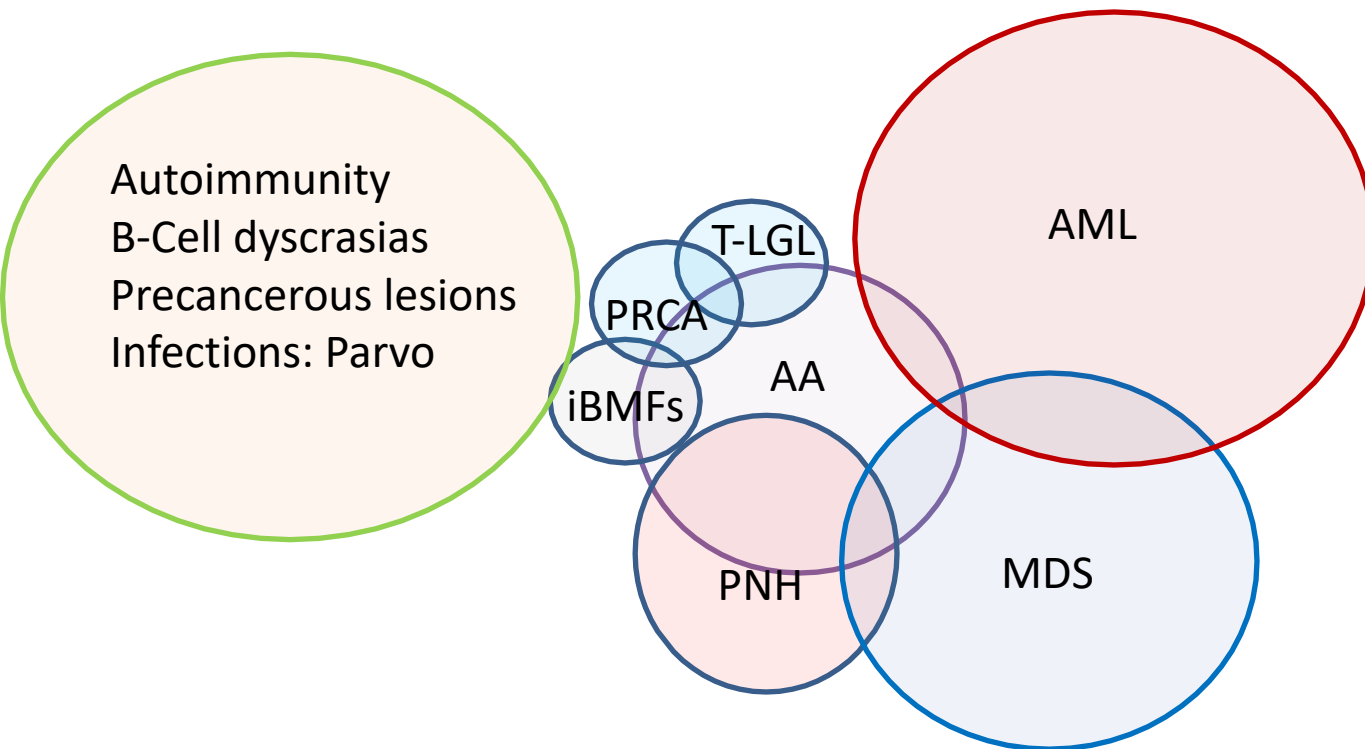


Learning Objectives

- Review evidence-based treatment approaches for frontline and relapsed/refractory SAA in adults and children
- Summarize the efficacy of TPO agonists in SAA
- Discuss and describe emerging therapies and clinical trials for PNH patients



Aplastic Anemia: Overlapping bone marrow failure states



INFLAMMATION, CLONAL HEMATOPOIESIS, EVOLUTION

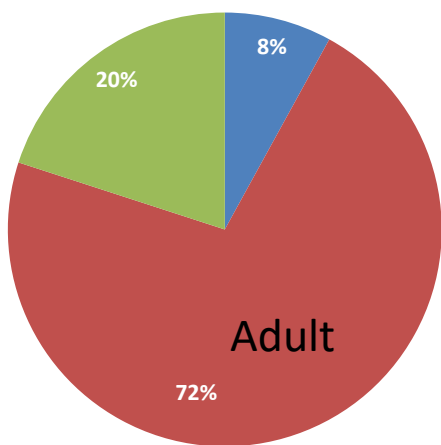
- Aplastic anemia is an enigmatic disease that highlights interplay of genetic events with autoimmunity/inflammation.
- Success of IST is the strongest evidence of immune pathogenesis
- Clonal evolution to AML is the strongest evidence of clonal nature of AA.



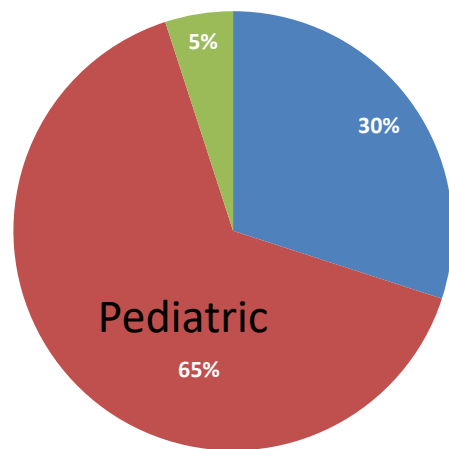
AA: Presentation and classification

- AA disease course can range from be fulminant or indolent.
- Hypoplastic MDS vs AA is a great diagnostic dilemma.

■ Inherited ■ Acquired ■ unknown



■ Inherited ■ Acquired ■ unknown



Camitta et al, Blood 1975

ACQUIRED

- ❖ Primary
- ❖ Secondary
 - Viral
 - Drug induced
 - Autoimmune
 - Radiation
 - GVHD
 - Pregnancy

INHERITED

- Fanconi Anemia
- Shwachman-Diamond syndrome
- Dyskeratosis congenita
- Diamond-Blackfan anemia
- Thrombocytopenia and absent radii syndrome

	<u>Very severe</u> AA	Severe AA	Moderate AA
cellularity	< 25%	< 25%	< 25%
ANC ($\times 10^9/L$)	< 200	< 500	> 500
retic count ($\times 10^9/L$)	< 60		
Platelet ($\times 10^9/L$)	< 10	< 20	> 20



Case 1

A **42-year-old** man presents to the emergency room with bruising and bleeding gums.

- CBC shows WBC 2.5k/ μ L, Hb 2.5 g/dL, platelets < 10k/ μ L, reticulocytes 10k/ μ L (0.2%), neutrophils 0.2k/ μ L.
- Chemistry, liver tests, and LDH are normal. B12 and folate are normal.
- **Bone marrow examination: cellularity 10%**. No dysgranulopoiesis or dysplastic megakaryocytes. No abnormal infiltrate. Reticulin grade 0-1 on WHO scale. Flow cytometry showed no myeloid or lymphoid neoplasm. **Karyotype normal.**
- **NGS** shows a pathogenic BCOR variant with VAF 2.5%.
- **PNH clone 3.1% of granulocytes.**

A diagnosis of SAA is made



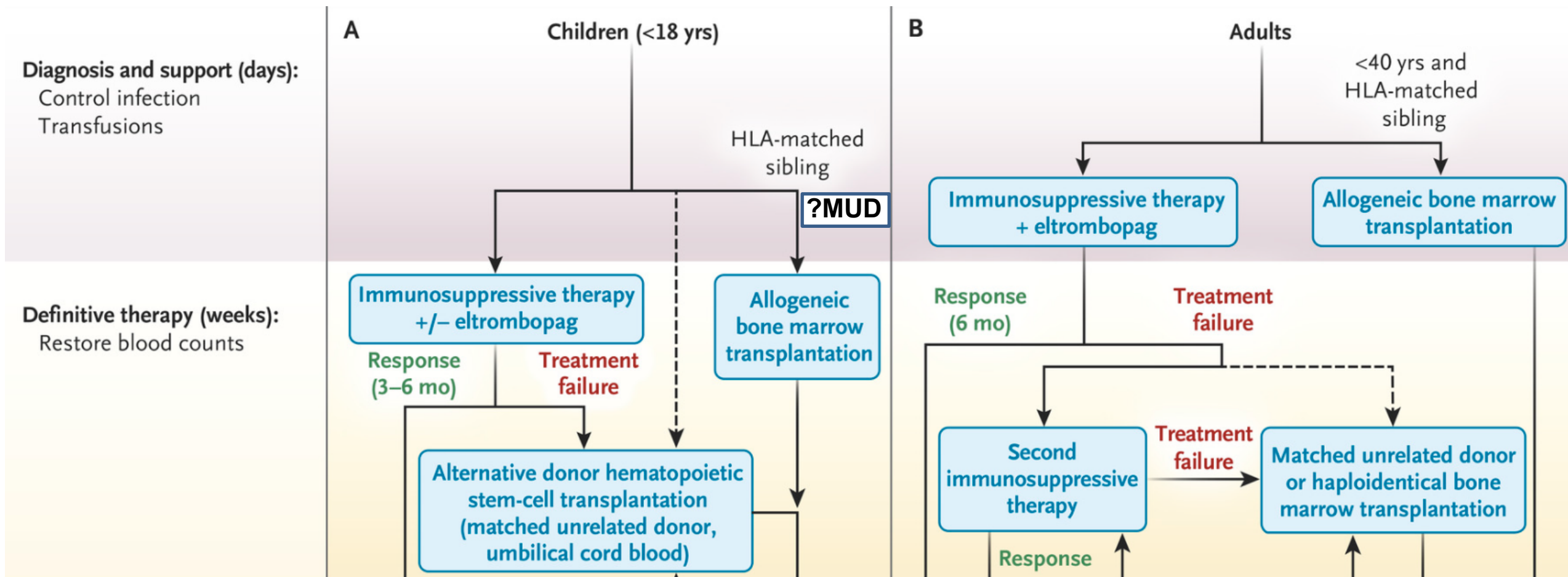
Audience Response Question

What front-line therapy would you recommend for this patient?

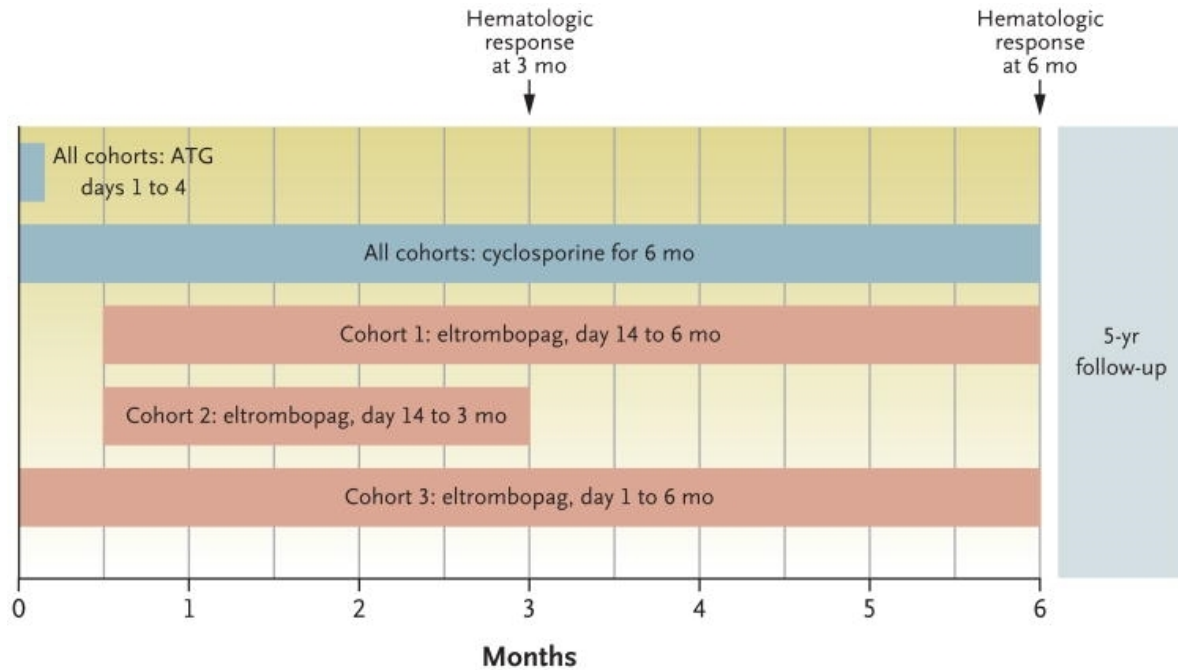
- a) Immunosuppressive therapy (IST) with horse ATG and cyclosporine A.
- b) Immunosuppressive therapy (IST) with horse ATG and cyclosporine A with eltrombopag.
- c) Upfront allogeneic hematopoietic stem cell transplant with matched related donor (MRD), if available.
- d) Upfront allogeneic hematopoietic stem cell transplant with best matched alternative donor (matched unrelated or haploidentical).
- e) Low intensity therapy with cyclosporine and eltrombopag.
- f) Corticosteroids, transfusions, and G-CSF support.



Treatment approach to Severe Aplastic Anemia (SAA)



hATG/CSA + eltrombopag



Overall response rates at 6 months were 80%, 87%, and 94%, respectively.

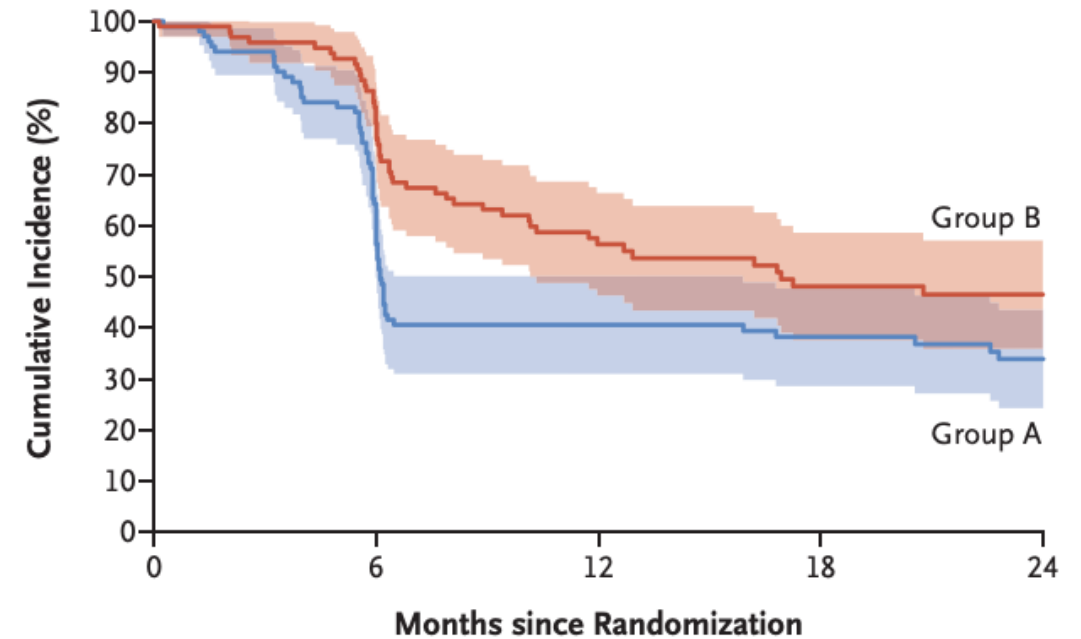
The complete and overall response rates in the combined cohorts were higher than historical cohort, with complete response was 10% and the overall response rate was 66%

Hematologic response	at 3 months	at 6 months	
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001



Characteristic	Group A: Horse ATG– Cyclosporine (N=101)	Group B: Horse ATG– Cyclosporine– Eltrombopag (N=96)	All Patients (N=197)
Follow-up — mo			
Median	24	23	24
95% CI	23–24	19–24	23–24
Age — yr			
Median	52	55	53
Range	15–81	16–77	15–81

- Achieved primary end point CR @ 3 months was higher with EPAG OR: 3.2, p=0.01
- Higher response at 6 months (61%)
- Faster time to response (3 vs. 8 months)
- Reintroduction of EPAG was the most common event in the experimental group



No. at Risk					
Group B	96	76	45	31	15
Group A	101	60	38	30	10

Can longer duration of EPAG be of benefit?

PROLONGED USE OF ELTROMBOPAG IN PATIENTS WITH SEVERE APLASTIC ANEMIA WITHOUT COMPLETE RESPONSE AT 6 MONTHS AFTER IMMUNOSUPPRESSIVE THERAPY

Ruixin Li¹, Qiqiang Long², Yan Yang³, Shengyun Lin⁴, Jinsong Jia⁵, Donghua Zhang⁶, Guangsheng He¹ and Jianyong Li¹

¹ the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; ² the Second Hospital of Nanjing, Nanjing, China; ³ the Hospital of Jilin University, Changchun, China; ⁴ the First Affiliated Hospital of Zhejiang TCM University, Hangzhou, China; ⁵ Peking University People's Hospital, Beijing, China; ⁶ Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China.



Key inclusion criteria

Age > 2 years

SAA or VSAA

Hypocellular BM without evidence of fibrosis or malignant cells

Therapeutic regimen: IST + EPAG

Rabbit ATG (3.5mg/kg/d for 5 days)

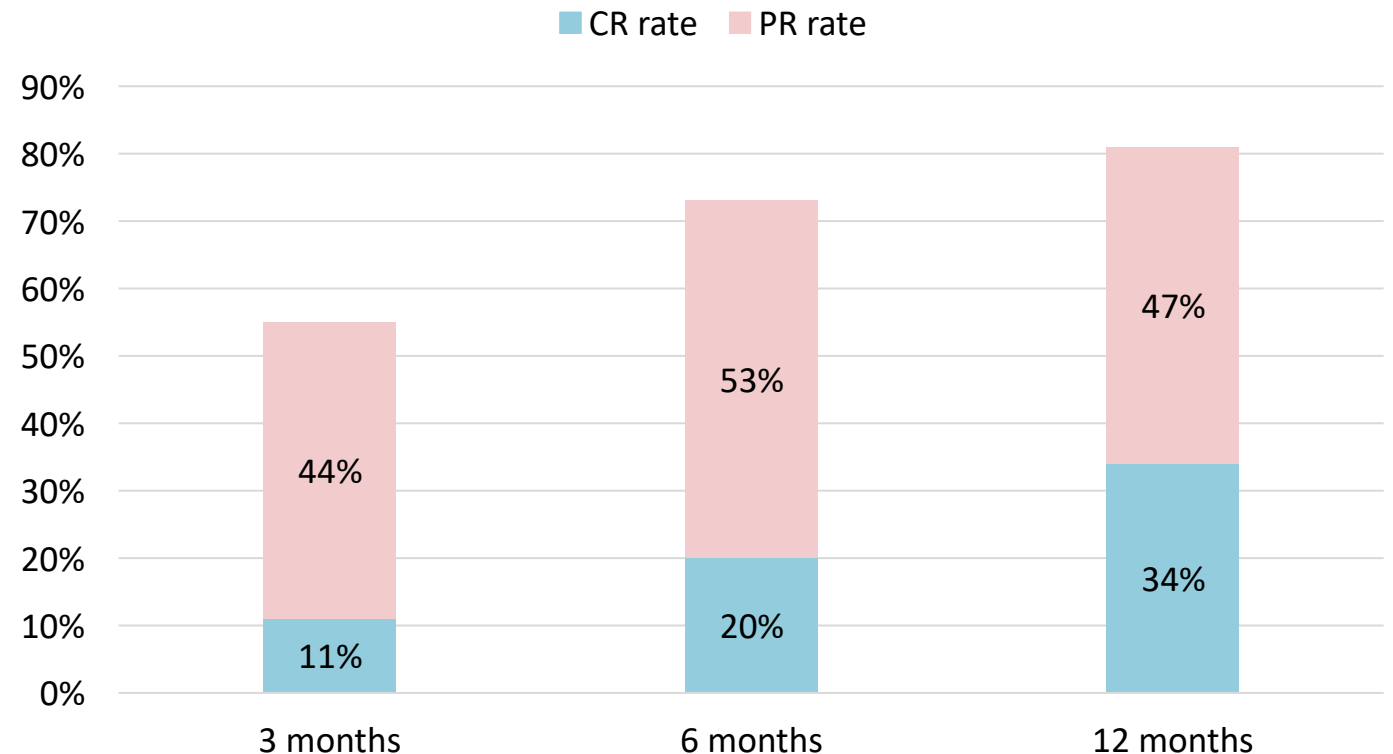
CsA (5 mg/kg/day)

Eltrombopag:

75 mg/d (>12 years old);

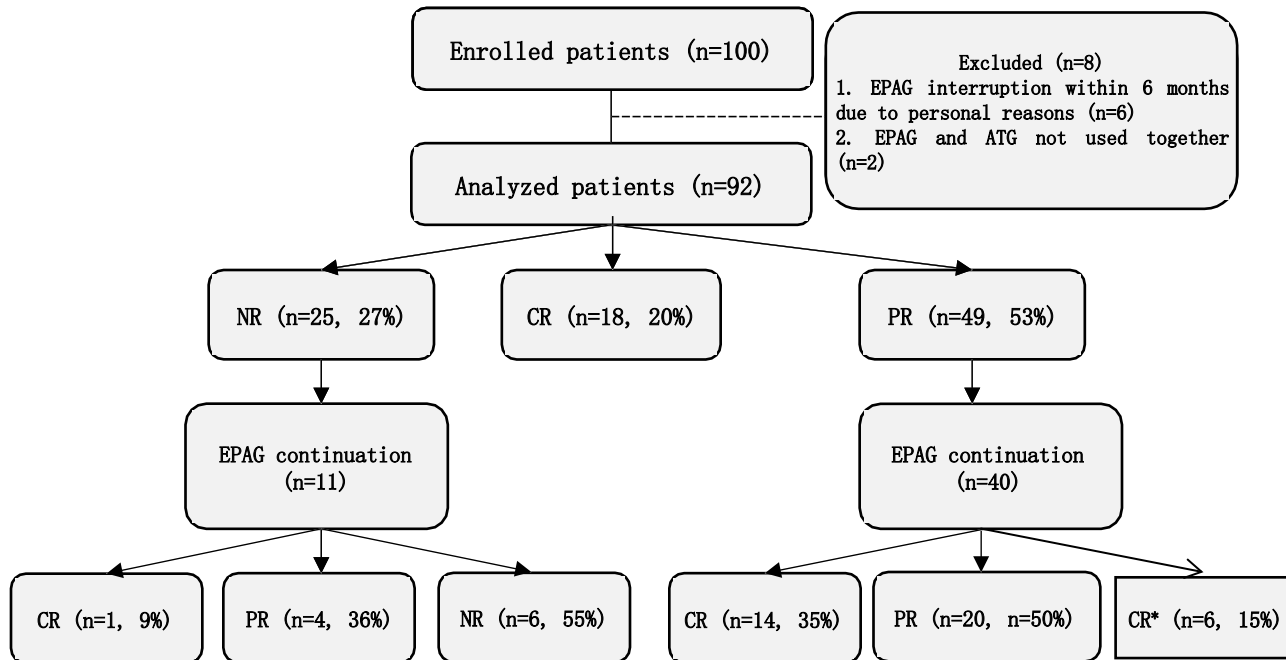
37.5 mg/d (6-11 years old);

1.25 mg/kg/d (2-5 years old)

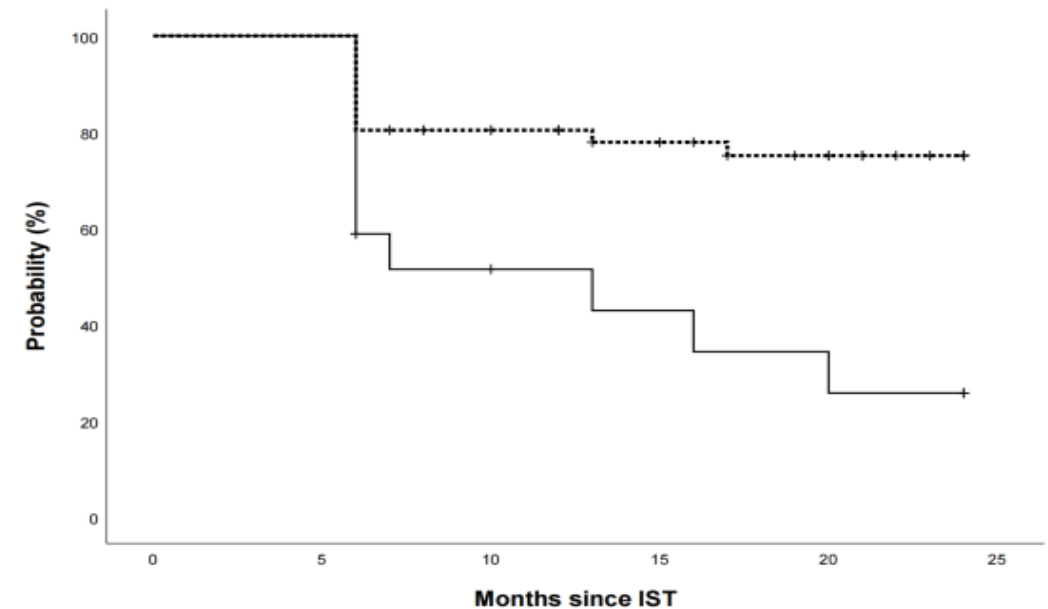


Can longer duration of EPAG be of benefit?

Study outcomes

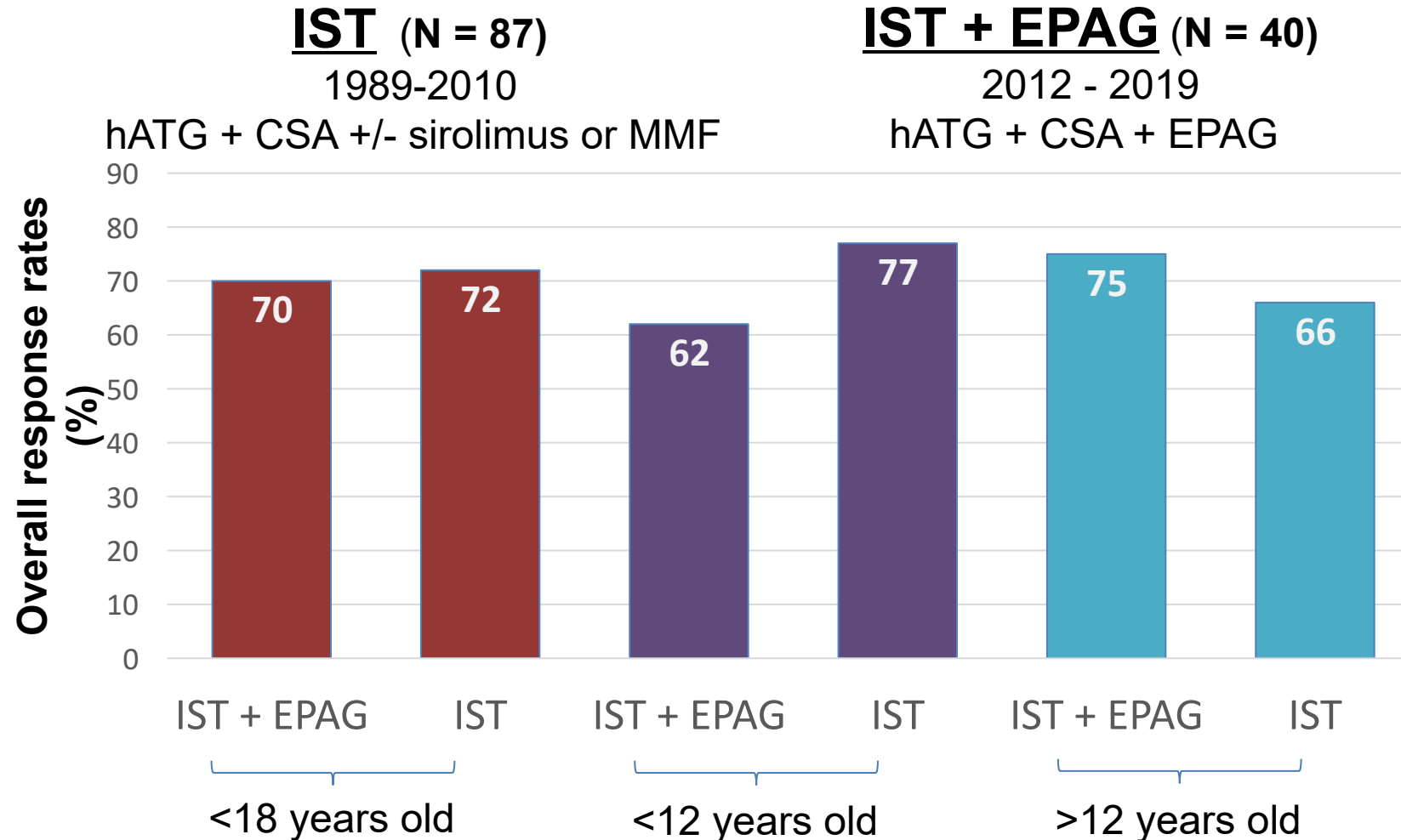


Event-free survival



Improved 2-year event-free survival in patients with PR and NR who continued EPAG after 6 months (75% vs. 26%, $P=0.001$).

Is there a benefit from adding eltrombopag to standard IST in pediatric SAA?





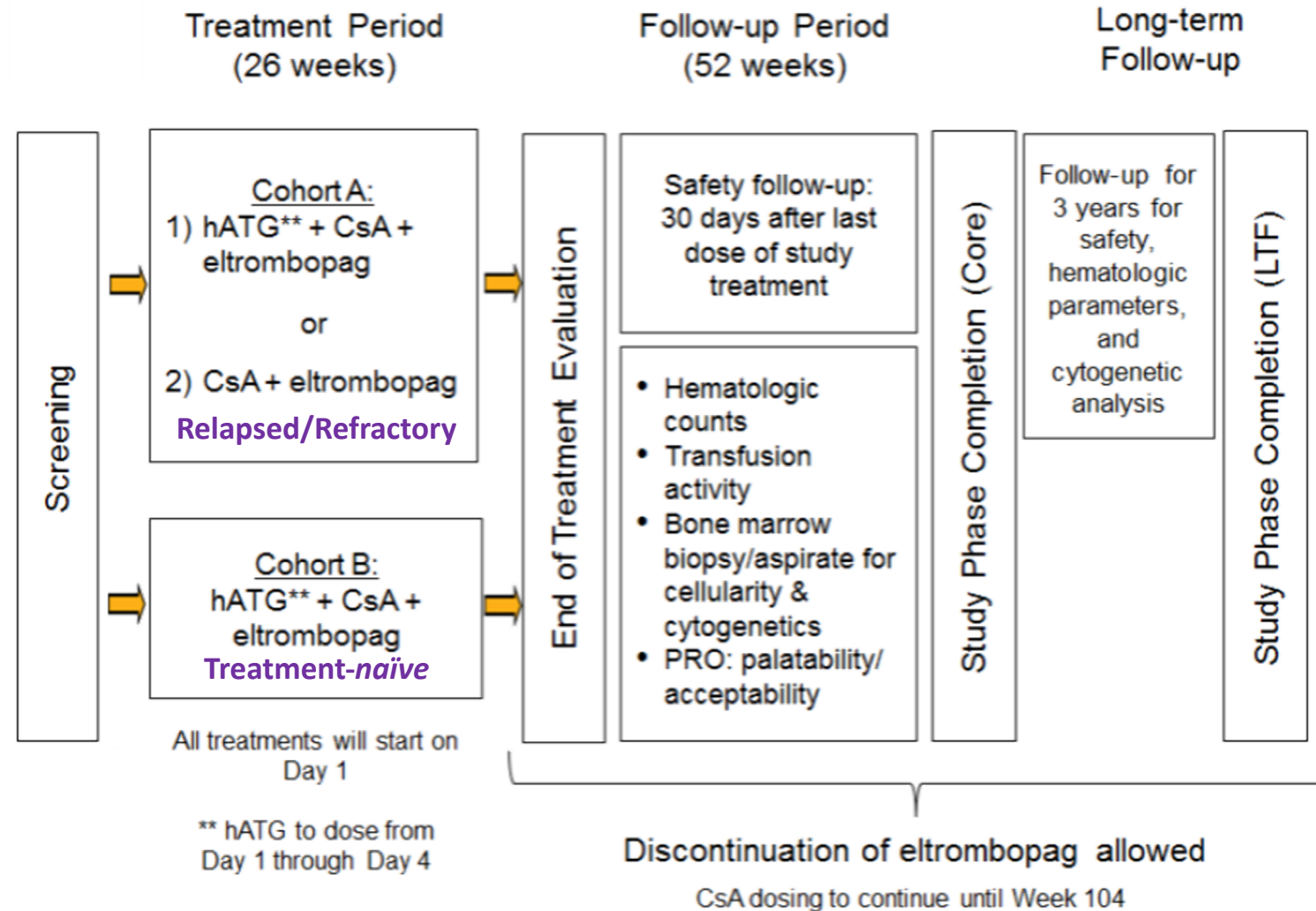
Eltrombopag in Pediatric Patients With Previously Untreated or Relapsed/Refractory Severe Aplastic Anemia: The Phase II ESCALATE Trial

Akiko Shimamura¹, Alexey Maschan², Carolyn Bennett³, Jason Farrar⁴, Sujith Samarasinghe⁵, Brigitte Strahm⁶, Winfred Wang⁷, Adrianna Vlachos⁸, Charlotte Niemeyer⁶, Timothy Olson⁹, Denise D'Alessio¹⁰, Elise Burmeister Getz¹¹, Tomasz Lawniczek¹², Yunnan Xu¹³, David A. Williams¹

¹Dana Farber and Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; ²Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia; ³Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA, USA; ⁴Arkansas Children's Research Institute and University of Arkansas for Medical Sciences, Little Rock, AR, USA; ⁵Department of Paediatric Haematology, Great Ormond Street Hospital for Children, London, UK; ⁶Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ⁷Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN, USA; ⁸Division of Hematology/Oncology and Cellular Therapy, Cohen Children's Medical Center, Northwell Health, New York, NY, USA; ⁹Department of Pediatrics, Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; ¹⁰Novartis Services Inc., East Hanover, NJ, USA; ¹¹Novartis Institutes for BioMedical Research (NIBR), Emeryville, CA, USA; ¹²Novartis Pharma AG, Basel, Switzerland; ¹³Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

Study Design: ESCALATE (NCT03025698)

- Phase II dose-escalation study to evaluate eltrombopag +IST in children with **relapsed/refractory (R/R) or treatment-naïve** severe aplastic anemia (SAA):
 - Pharmacokinetics
 - Safety
 - Efficacy
 - Acceptability of eltrombopag
- The eltrombopag **starting dose of 50 mg/day (25 mg/day in patients <6 years)** was titrated to **goal dose of 150 mg/day** to achieve a platelet count of 50–200 × 10⁹/L
- Data cut-off for this analysis is 78 weeks



Patient Disposition

	R/R SAA	TN SAA	All patients
Patients	n=14 n (%)	n=37 n (%)	N=51 n (%)
Enrolled and treated	14 (100)	37 (100)	51 (100)
Completed 26-week treatment phase	11 (78.6)	25 (67.6)	36 (70.6)
Completed 52-week follow-up period	8 (57.1)	18 (48.6)	26 (51.0)
Entered 3-year follow-up period	9 (64.3)	19 (51.4)	28 (54.9)
Continuing 3-year follow-up period	8 (57.1)	16 (43.2)	24 (47.1)
Ongoing treatment with eltrombopag	2 (14.3)	3 (8.1)	5 (9.8)
Discontinued eltrombopag	6 (42.9)	20 (54.1)	26 (51.0)
Reasons for eltrombopag discontinuation (n=26, 51.0%)			
Physician decision	2 (14.3)	9 (24.3)	11 (21.6)
Adverse event	3 (21.4)	4 (10.8)	7 (13.7)
Patient/guardian decision	0	4 (10.8)	4 (7.8)
No longer requires treatment	1 (7.1)	2 (5.4)	3 (5.9)
Progressive disease	0	1 (2.7)	1 (2.0)

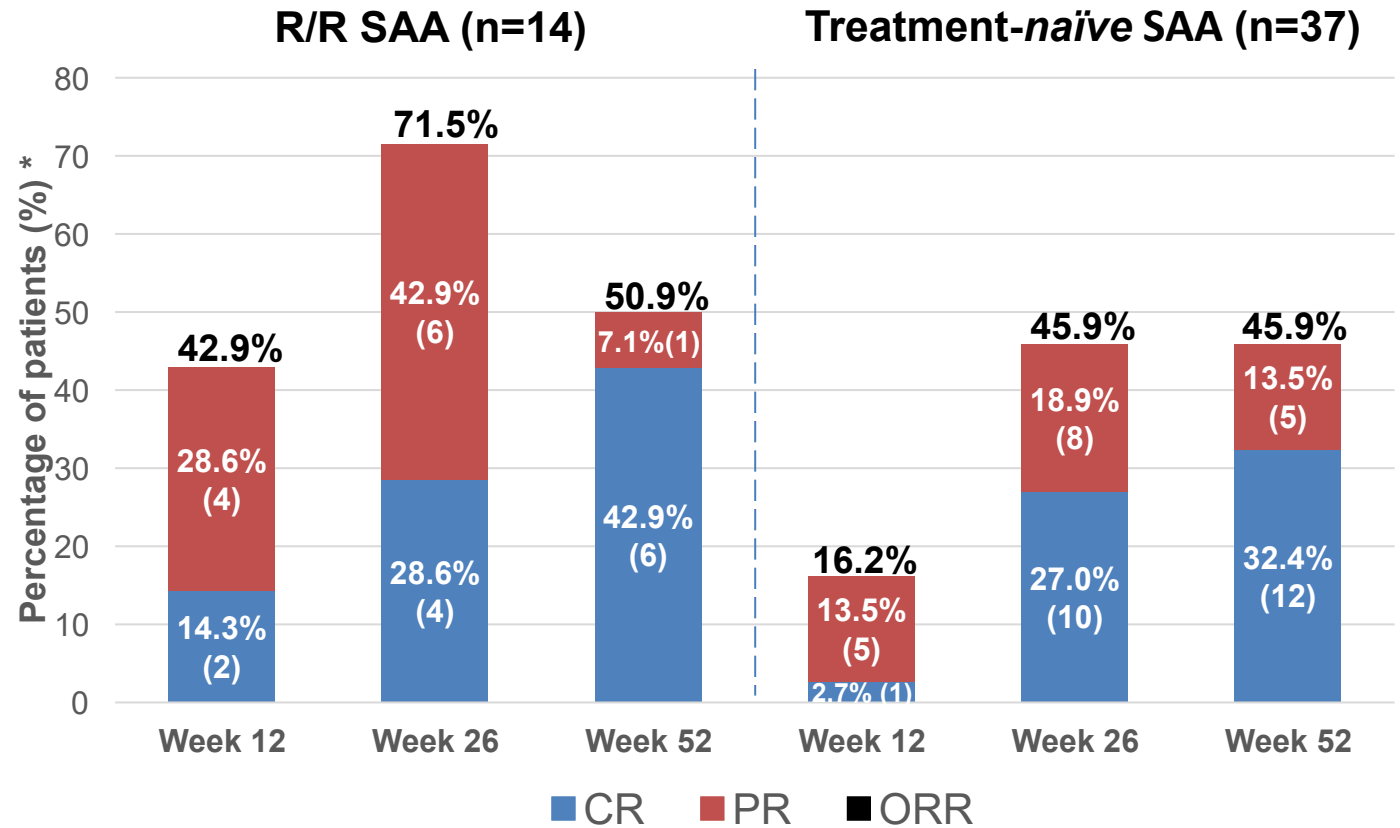
Overall response rate

Complete response (CR):

- Transfusion independent[†]
- Hemoglobin ≥ 10 g/dL
- Absolute neutrophil count $\geq 1 \times 10^9/L$
- Platelet count $\geq 100 \times 10^9/L$

Partial response (PR):

- Transfusion independent[†]
- Hemoglobin ≥ 8 g/dL
- Absolute neutrophil count $\geq 0.5 \times 10^9/L$
- Platelet count $\geq 20 \times 10^9/L$



Safety and tolerability

- The treatment-related AE reported were consistent with the known safety profiles of hATG, CsA, and eltrombopag
- AEs leading to treatment discontinuation included*:
 - ALT increase (n=4, 7.8%)
 - AST increase (n=3, 5.9%)
 - Blood bilirubin increase (n=2, 3.9%)
 - Drug-induced liver injury (n=1, 2.0%)

Most common treatment-related AEs (≥10% of patients)

Adverse event by preferred term	R/R SAA n=14		TN SAA n=37		All patients N=51	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with ≥1 event	14 (100)	5 (35.7)	37 (100)	12 (32.4)	51 (100)	17 (33.3)
Blood bilirubin increased	6 (42.9)	2 (14.3)	16 (43.2)	2 (5.4)	22 (43.1)	4 (7.8)
ALT increased	8 (57.1)	0	13 (35.1)	5 (13.5)	21 (41.2)	5 (9.8)
Blood creatinine increased	7 (50.0)	0	13 (35.1)	0	20 (39.2)	0
AST increased	6 (42.9)	0	11 (29.7)	4 (10.8)	17 (33.3)	4 (7.8)
Hypertension	3 (21.4)	1 (7.1)	13 (35.1)	2 (5.4)	16 (31.4)	3 (5.9)
Hypomagnesaemia	3 (21.4)	0	10 (27.0)	0	13 (25.5)	0
Blood urea increased	6 (42.9)	0	6 (16.2)	0	12 (23.5)	0
Nausea	2 (14.3)	0	8 (21.6)	0	10 (19.6)	0
Serum sickness	2 (14.3)	0	7 (18.9)	1 (2.7)	9 (17.6)	1 (2.0)
Acute kidney injury	3 (21.4)	0	5 (13.5)	2 (5.4)	8 (15.7)	2 (3.9)
Vomiting	2 (14.3)	0	4 (10.8)	0	6 (11.8)	0

Conclusions

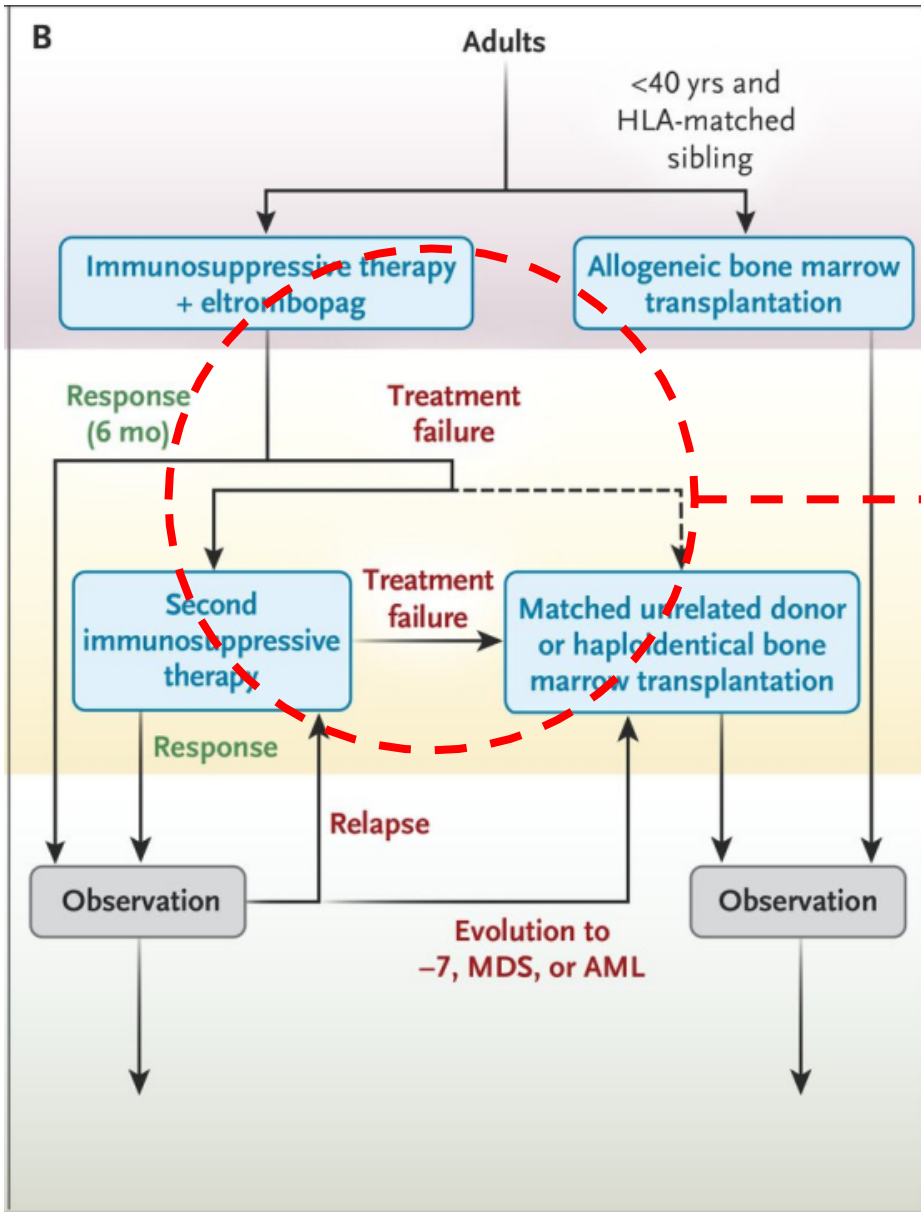
- Most pediatric patients received the 150 mg/day maximum daily dose of eltrombopag, consistent with daily doses recommended in adult patients
- The overall response rate was up to 71.5% in pediatric patients with R/R SAA and up to 45.9% in those with treatment-*naïve* SAA
- Eltrombopag is a well tolerated treatment option for pediatric patients with R/R or treatment-*naïve* SAA
 - AEs observed were consistent with safety profiles of hATG, CsA and eltrombopag
- Pharmacokinetics of eltrombopag in pediatric patients with SAA showed relatively higher exposure in younger (1 to <6 years) versus older (6 to <18 years) patients
 - The trend of decreasing exposure with age is consistent with the pharmacokinetics observed in adult patients with SAA
- **NAPAAC not recommending EPAG with IST as SOC for pediatric patients as similar responses achieved with hATG/CSA alone**

Case 1 Continued

Despite receiving hATG/CSA/EPAG the patient's counts remain low and he remains transfusion dependent. Repeat bone marrow shows hypocellular marrow (10%), no dysplasia, and a normal karyotype.

What are the next steps?





Next step for relapsed/refractory patients?

Transplant

OR

2nd course of immunosuppressive therapy

OR

?? Alternate TPO agonists





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Efficacy and Safety of Long-term Romiplostim Use for Refractory AA

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¹Department of Hematology and Oncology, Dokkyo Medical University, Tochigi, Japan; ²Division of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; ³Department of Hematology, Sungkyunkwan University Samsung Medical Center, Seoul, Republic of Korea; ⁴Department of Blood Transfusion, Osaka University Hospital, Osaka, Japan; ⁵Department of Transfusion and Cell Transplantation, Kitasato University School of Medicine, Sagami-hara, Japan; ⁶Department of Hematology, Kurume University Hospital, Kurume, Japan; ⁷Department of Hematology, NTT Medical Center Tokyo, Tokyo, Japan; ⁸Department of Hematology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan; ⁹Department of Internal Medicine, Matsuyama Red Cross Hospital, Matsuyama, Japan; ¹⁰Department of Hematology, Ogaki Municipal Hospital, Ogaki, Japan; ¹¹Department of Hematology and Rheumatology, Kindai University Faculty of Medicine, Osaka, Japan; ¹²Department of Hematology, Saitama Medical Center, Saitama Medical University, Saitama, Japan; ¹³Department of Hematology and Oncology, Anjo Kosei Hospital, Anjo, Japan; ¹⁴Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; ¹⁵Department of Hematology, Sapporo Hokuyu Hospital, Sapporo, Japan; ¹⁶Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai, Japan; ¹⁷Department of Transfusion Medicine and Cell Therapy, Kumamoto University Hospital, Kumamoto, Japan; ¹⁸Biostatistics Center, Kurume University, Kurume, Japan; ¹⁹Kyowa Kirin Co., Ltd., Tokyo, Japan; ²⁰Department of Hemato-Oncology, International Medical Center, Saitama Medical University, Saitama, Japan; ²¹Division of Hematology, Jichi Medical University, Tochigi, Japan; ²²Division of Transfusion Medicine, Kanazawa University Hospital, Kanazawa, Japan

Hematological responses with romiplostim at Weeks 27 and 53 (N = 31)

Hematological endpoint	No. of responders (%) [95% CI]	
	Week 27	Week 53
Any hematological response	26 (84) [66–95]	25 (81) [63–93]
Platelet response	20 (65) [45–81]	20 (65) [45–81]
Erythroid response	23 (74) [55–88]	21 (68) [49–83]
Neutrophil response	12 (39) [22–58]	15 (48) [30–67]
Trilineage response	8 (26) [12–45]	12 (39) [22–58]

In total, median (95% CI) time from the first administration to hematological response was 37.0 (36.0, 44.0) days.

J.H. Jang et al., *Br. J. Haematol.* 2021; 192: 190-9.

◆ However, long-term efficacy and safety data of romiplostim in refractory AA beyond 53 weeks are scarce.

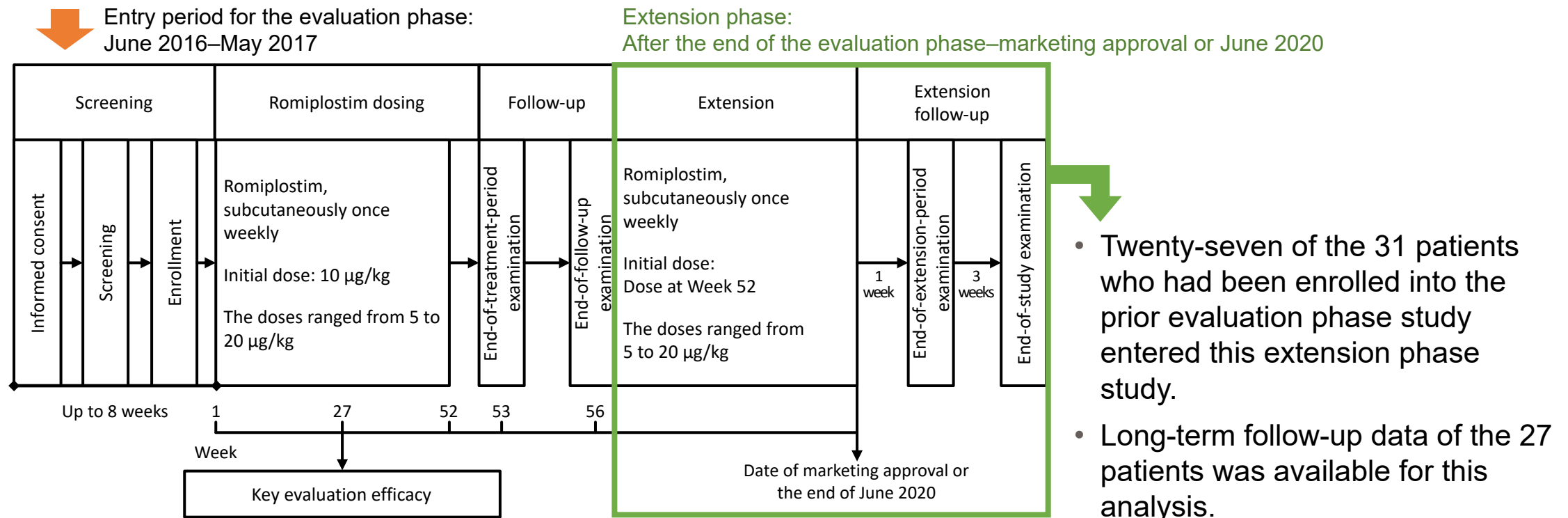
➔ In this study, we evaluated the efficacy and safety of romiplostim during long-term administration after 53 weeks.

Study design and methods

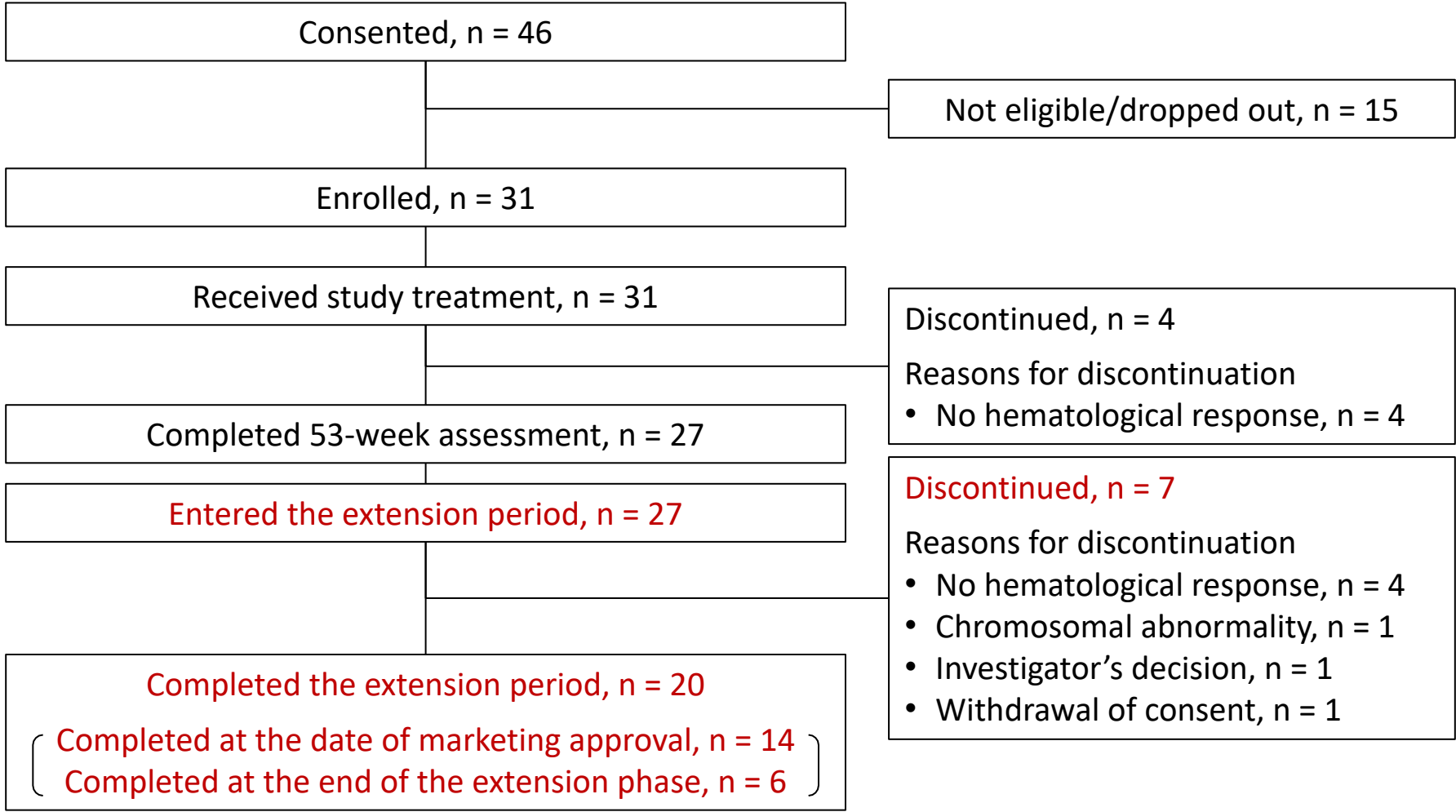
◆ Key Eligibility Criteria

Patients:

- with AA who were refractory to immunosuppressive treatment or ineligible for anti-human thymocyte globulin treatment and refractory cyclosporin A
- with platelet counts of $\leq 30 \times 10^9/L$
- with ECOG PS scores of 0 to 2 at screening
- aged ≥ 20 (Japan) and ≥ 19 years (Korea)



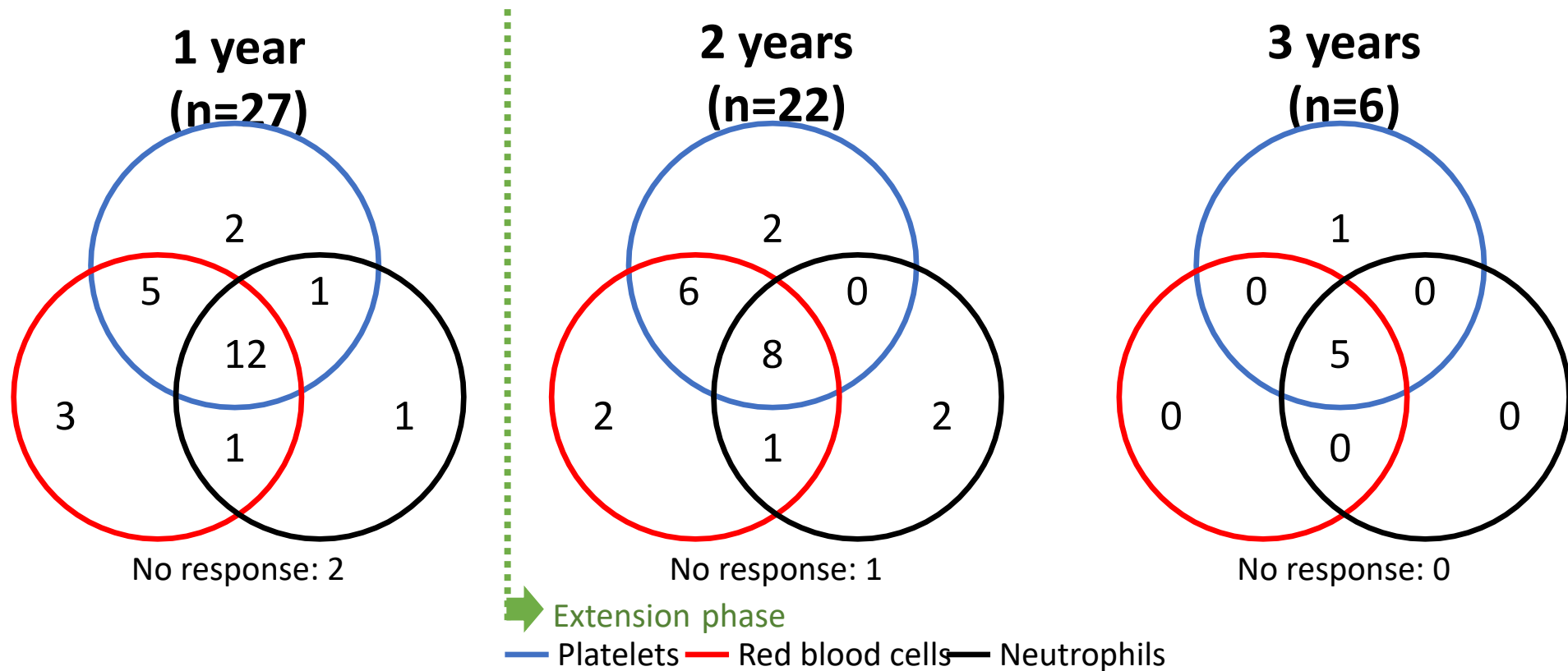
Patients treated



*Red indicates extension period.



Hematological responses to romiplostim at 1, 2, and 3 years



- ❖ Long term (42 months or 3.5 years) follow-up study of romiplostim administration in adult patients with refractory AA demonstrated its safety and efficacy during the extension period.
- ❖ Presence of late responders to romiplostim demonstrated

What are the outcomes with upfront haploidentical BMT for SAA?

Abstract #2123

ALTERNATIVE DONOR BONE MARROW TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE (PTCY) AS INITIAL THERAPY FOR ACQUIRED SEVERE APLASTIC ANEMIA #2123

Amy E DeZern¹, MD, MHS, Marianna Zahurak¹, MS, Kenneth Cooke¹, MD, Richard J Jones¹, MD, Robert A. Brodsky¹, MD
1. Johns Hopkins, Baltimore, MD, USA



Use of upfront haploidentical BMT in SAA

Patients met SAA criteria. IBMFS excluded

Non-myeloablative conditioning:

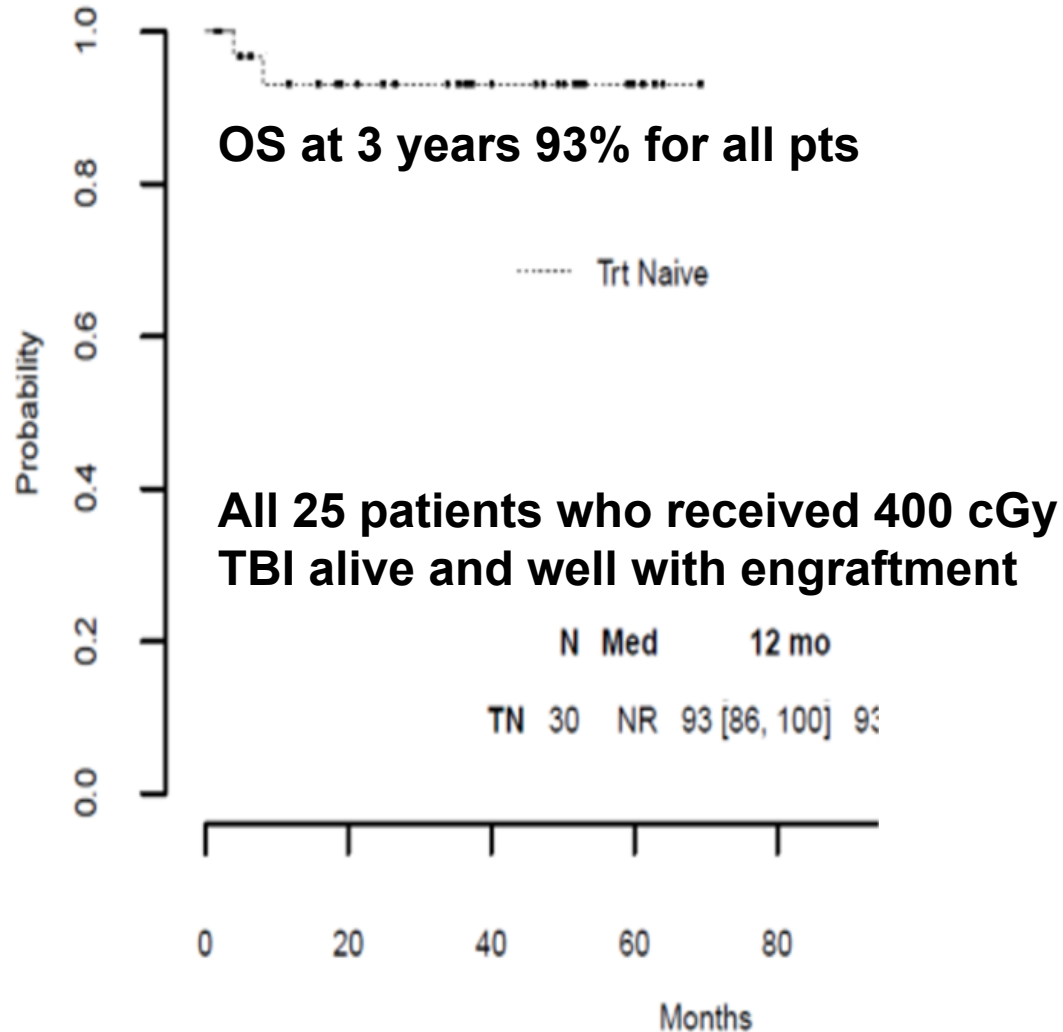
- Rabbit ATG (0.5 mg/kg day-9 and 2 mg/kg on days -8,-7),
- Fludarabine (30mg/m²/day on days -6 to -2),
- Low dose CY (14.5 mg/kg on days -6, -5) and
- Total body irradiation (200cGy or 400 cGy day -1).

GVHD prophylaxis:

- Cyclophosphamide 50 mg/kg/day IV D+3, D+4
- MMF day 5-35
- tacrolimus day 5 through D180 or 1 year.

<u>PATIENT DEMOGRAPHICS</u>	<u>TREATMENT-NAÏVE (n=32)</u>
Median age (range, years)	25 (3-63)
Male	18 (56%)
vSAA	15 (48%)
Presence of Clonality at BMT	23/31 (74%)
Self-identified as minority	33%
<u>DONORS</u>	
Median age (range, years)	31 (13-55)
Male	58%
Haplo sibling	7
Biological parent	6
Biological child	7
Haplo 2° relative	7
MSD or 10/10 unrelated donor	5

Use of upfront haploidentical BMT in SAA



N=32

Engraftment:

- Median time ANC recovery 20 days (range 14-88)
- Median time RBC recovery 25 days (90% TI D60)
- Median time PLT 25 days (90% TI D100)

• **3 graft failures when 200cGy TBI used**

GVHD:

- 7% for both acute and chronic



Abstract #193

Efficacy of JAK1/2 inhibition in murine immune bone marrow failure

Emma M. Groarke, Xingmin Feng, Nidhi Aggarwal, Ash Lee Manley, Zhijie Wu, Shouguo Gao, Bhavisha Patel, Jichun Chen, Neal S. Young

Hematology Branch

National Heart, Lung and Blood Institute

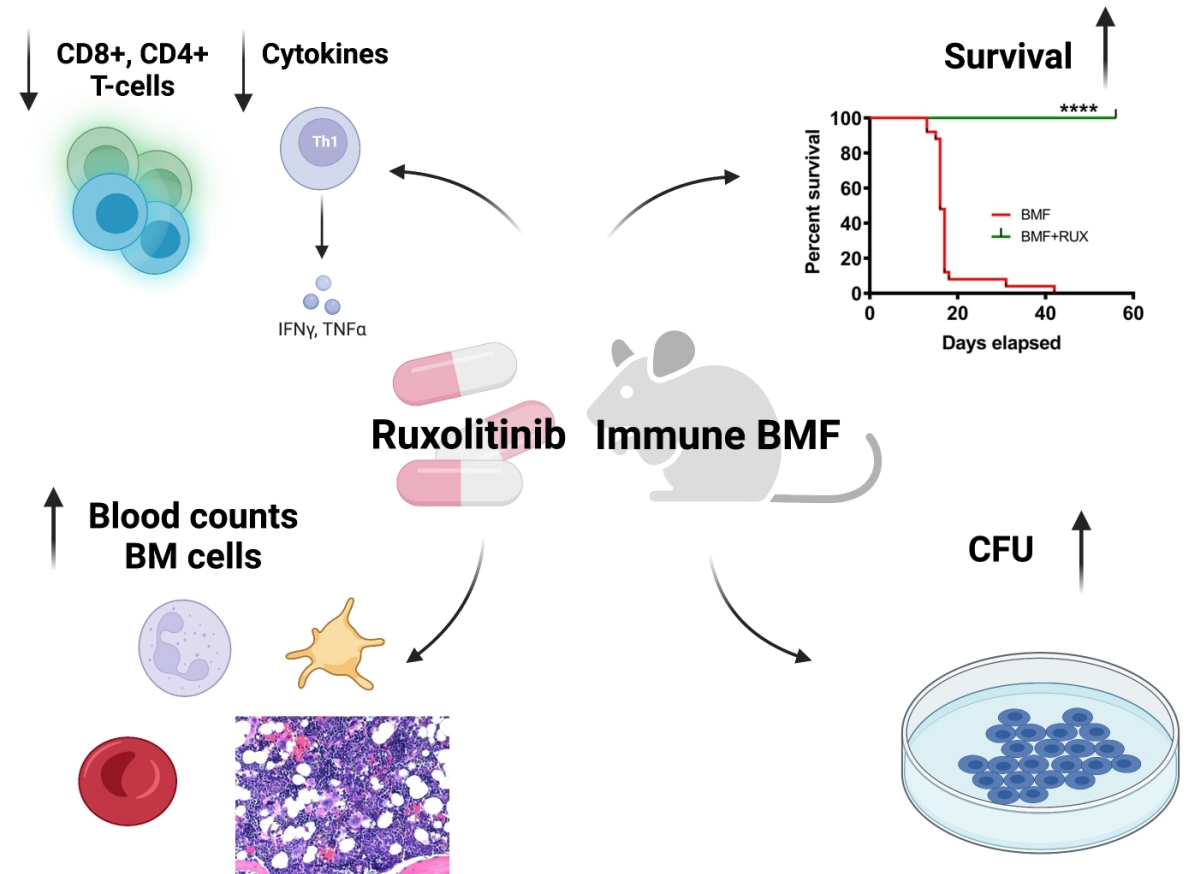
National Institutes of Health



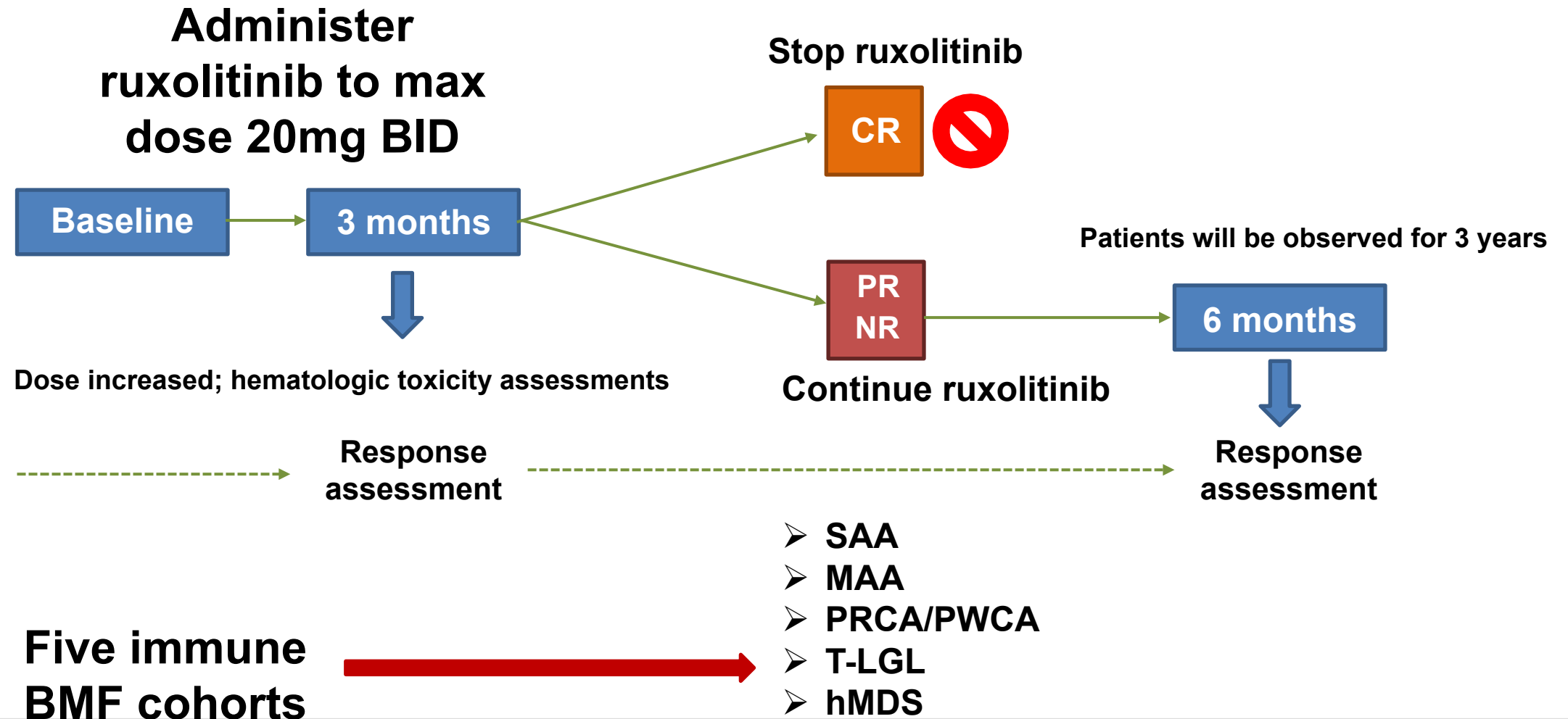
Ruxolitinib effectively treats murine BMF

In mouse model of immune BMF, ruxolitinib:

- Rescued blood counts
- T-cell (CD4/CD8) inhibition
- Decreased marrow apoptosis
- Increased residual marrow cell viability
- Increased T-regulatory cells
- Improved CFU
- Superior overall survival



A Phase I/II Study of the JAK1/2 Inhibitor Ruxolitinib for Relapsed / Refractory Immune Bone Marrow Failure



Clinical Trial of IL2R Ab ongoing

- Ongoing clinical study in AA to establish safety profile of REGN7257 and POC (NCT04409080)
- Open-label study in patients with severe AA whose disease is refractory to or relapsed on SoC IST and for whom a SCT is not available or suitable as a treatment option
- The first part of the study involves dose escalation cohorts to inform safety and pharmacologic considerations
- The second part involves an expansion cohort for both safety and proof of concept



Acquired Aplastic Anemia: Take Home Points

AA therapy in adults

- In adults >40 years, IST with EPAG remains SOC at this time.
- Romiplostim has shown efficacy in the relapsed / refractory setting

AA therapy in children

- Eltrombopag in combination with hATG/CSA still not an established SOC for pediatric patients with treatment-naïve SAA

Emerging therapies

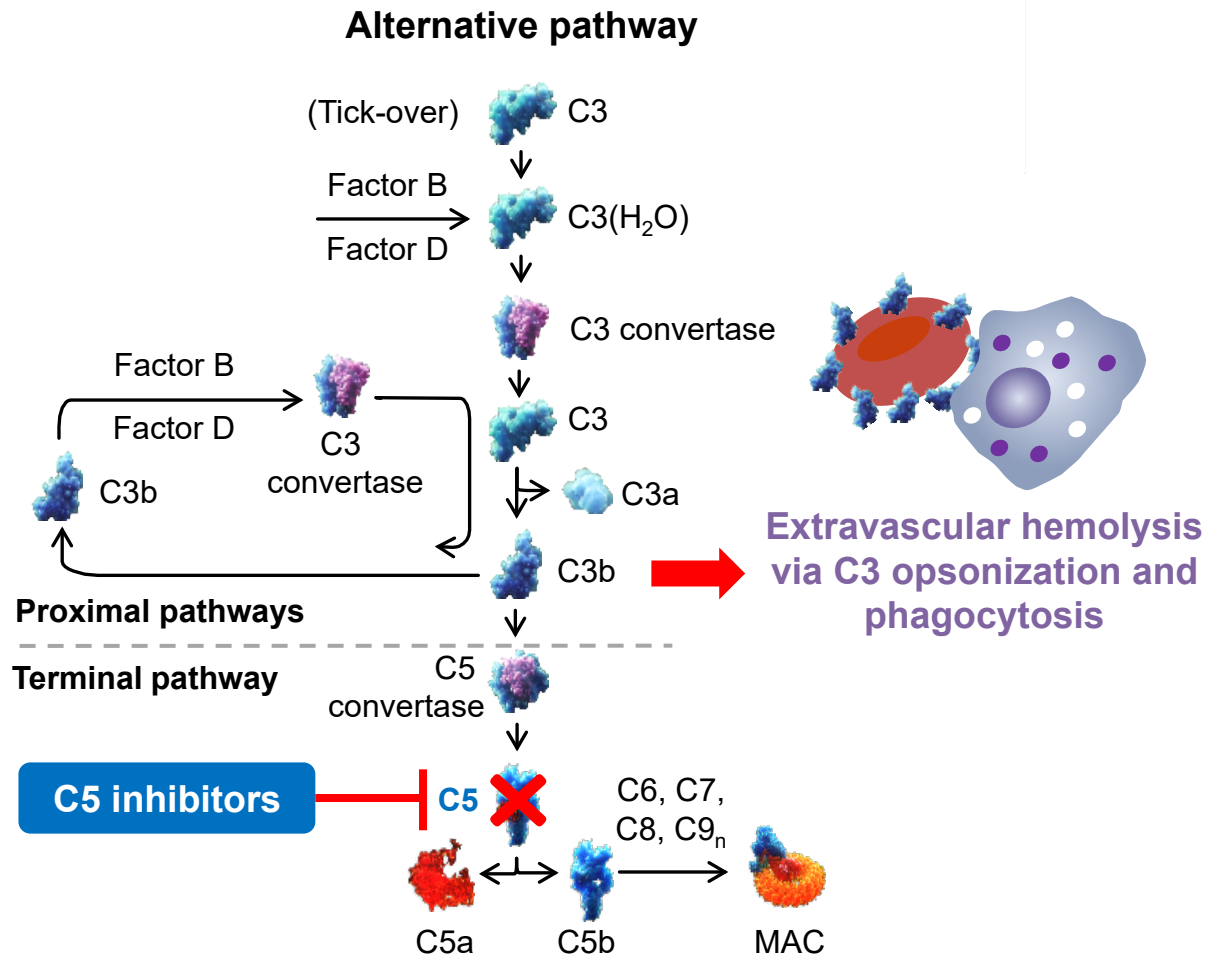
- IL2RG MAB effective in murine BMF – clinical trial currently under way (NCT04409080)
- JAK1/2 inhibition effective in murine BMF model – clinical trial coming soon



What are some of the new therapies in development for PNH?



Complement regulation in PNH is impaired



- PNH is a **rare, chronic hematological disorder** characterized by intravascular hemolysis, thrombophilia and bone marrow failure
- PNH is caused by a somatic mutation in the *PIGA* gene, resulting in a lack of the GPI-anchored complement-regulating proteins **CD55** and **CD59**, leading to **intravascular hemolysis**
- Targeting the **terminal complement pathway** at C5 with **SoC eculizumab and ravulizumab** controls intravascular hemolysis, reduces thrombosis and improves overall survival
- **Up to two-thirds** of patients have clinically meaningful residual anemia, largely because of emerging **extravascular hemolysis**; consequently, some patients are **transfusion dependent**



Oral monotherapy with iptacopan, a proximal complement inhibitor of factor B, has superior efficacy to intravenous terminal complement inhibition with standard of care eculizumab or ravulizumab and favorable safety in patients with paroxysmal nocturnal hemoglobinuria and residual anemia: Results from the randomized, active-comparator-controlled, open-label, multicenter, Phase III APPLY-PNH study

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Cécile Kerloeguen,²⁰ Rafael Levitch,²⁰ Rakesh Kumar,²¹ Christine Thorburn,²²
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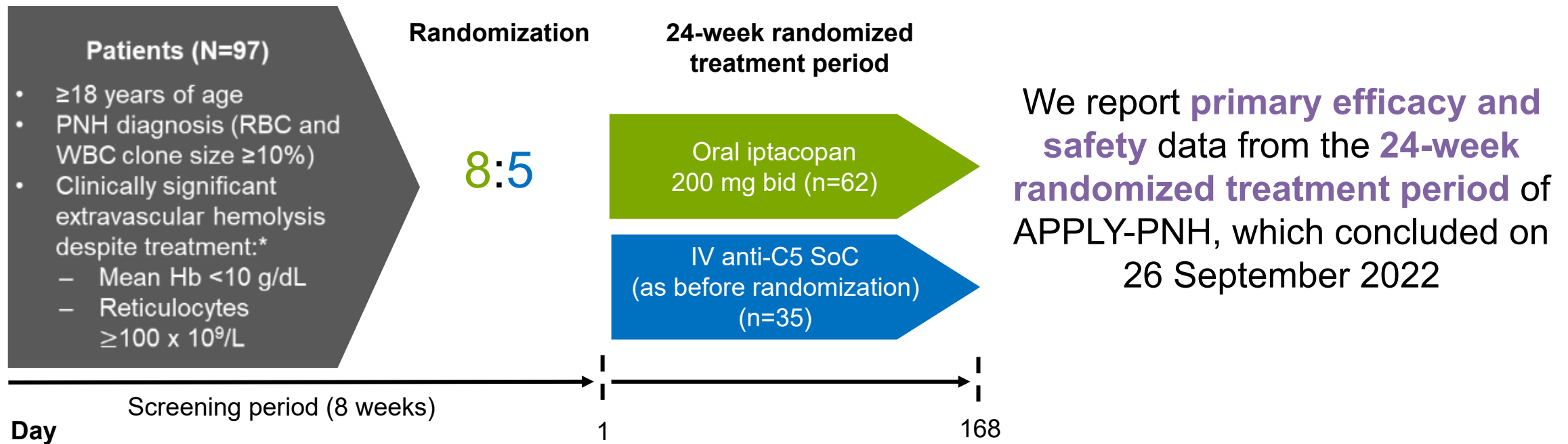
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- Slides
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APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan monotherapy in PNH patients with residual anemia despite SoC therapy (NCT04558918)



APPLY-PNH is a superiority trial with two primary endpoints

Primary

- Hematological response defined as an **increase from baseline in Hb of ≥ 2 g/dL in the absence of RBC transfusions**
- Hematological response defined as **Hb ≥ 12 g/dL in the absence of RBC transfusions**

Secondary

- **Transfusion avoidance**
- **Change from baseline:**
 - Hb levels
 - FACIT-Fatigue scores
 - Absolute reticulocyte count
 - LDH levels
- Occurrences of **clinical breakthrough hemolysis** and **MAVEs[§]**
- Safety

- A multiple testing procedure adjusting for multiplicity was used to determine superiority



Demographics and disease characteristics at baseline were generally balanced between arms

	Iptacopan 200 mg bid N=62	Anti-C5 SoC N=35	Overall N=97
Mean age, years (SD)	51.7 (16.9)	49.8 (16.7)	51.0 (16.8)
Female, n (%)	43 (69.4)	24 (68.6)	67 (69.1)
Time since diagnosis, years (SD)	11.9 (9.8)	13.6 (10.9)	12.5 (10.2)
Anti-C5 SoC			
Eculizumab,* n (%)	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab,* n (%)	22 (35.5)	12 (34.3)	34 (35.1)
Mean duration, years (SD)	3.8 (3.5)	4.2 (3.9)	4.0 (3.6)
Received RBC transfusions,* n (%)	35 (56.5)	21 (60.0)	56 (57.7)
Mean baseline Hb, g/dL (SD) [range]	8.9 (0.7) [6.8–10.0]	8.9 (0.9) [6.2–9.9]	8.9 (0.8) [6.2–10.0]
Mean baseline LDH, U/L (SD) [range]	269.1 (70.1) [150–539]	272.7 (84.8) [133–562]	270.4 (75.3) [133–562]
Baseline LDH >1.5 x ULN, n (%)	4 (6.5)	3 (8.6)	7 (7.2)
Mean baseline absolute reticulocyte count, 10 ⁹ /L (SD) [range]	193.2 (83.6) [51–563]	190.6 (80.9) [90–412]	192.3 (82.3) [51–563]

Iptacopan monotherapy was superior to SoC for both primary endpoints

Increase from baseline in Hb of ≥ 2 g/dL
in the absence of RBC transfusions

Hb ≥ 12 g/dL
in the absence of RBC transfusions

Observed

51/60*

patients treated
with **iptacopan**

0/35

patients treated
with **SoC**

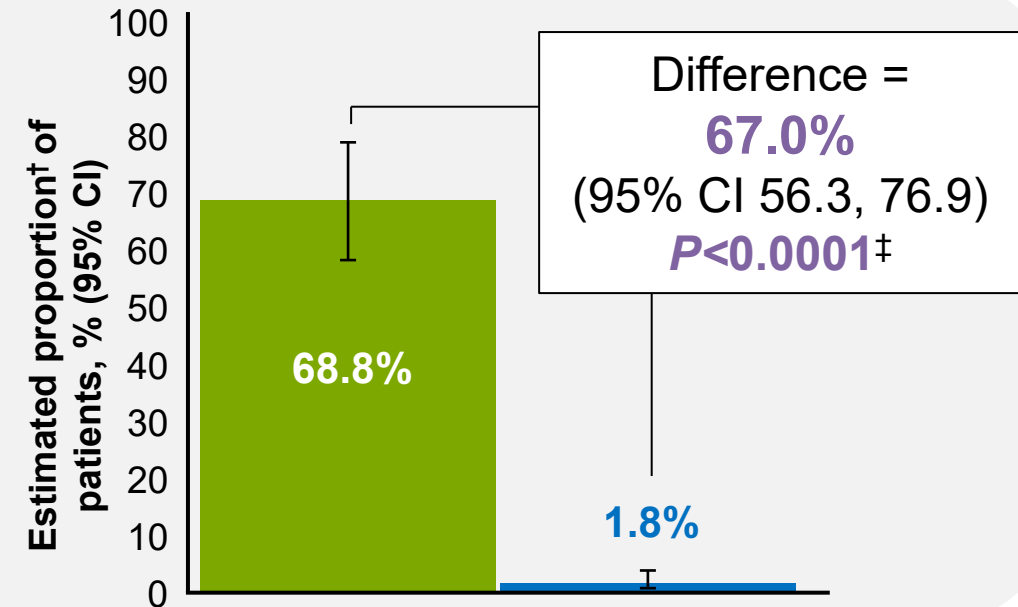
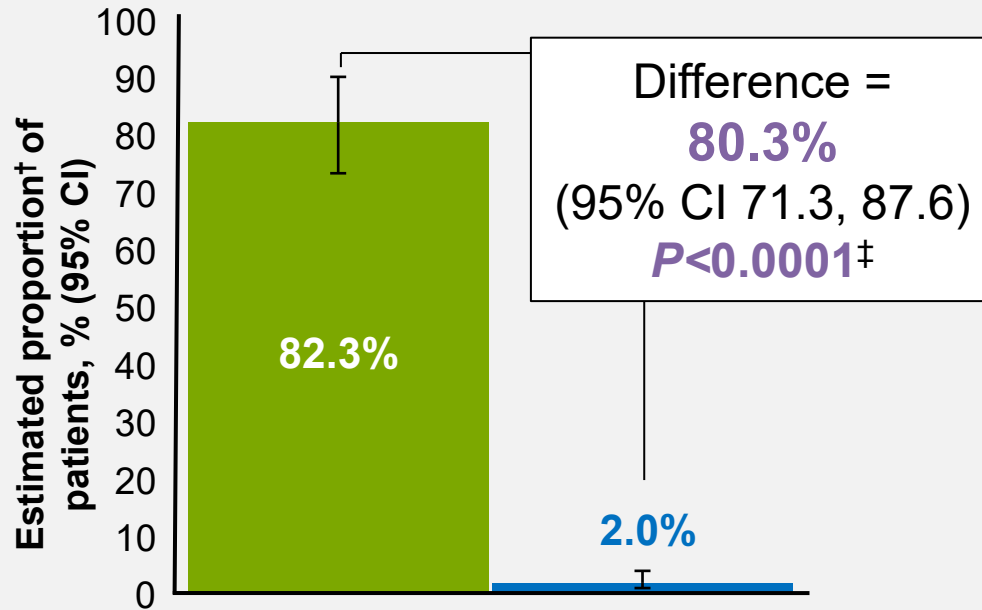
42/60*

patients treated
with **iptacopan**

0/35

patients treated
with **SoC**

Population
estimate



Iptacopan monotherapy was superior to SoC for rate of clinical breakthrough hemolysis and MAVEs

	Arm	n/N [†]	Adjusted annual rate, % (95% CI)	Rate ratio (95% CI) [‡]	P value [‡]
Rate of clinical breakthrough hemolysis*	Iptacopan	2/62	0.07 (0.02, 0.31)	0.10 (0.02, 0.61)	0.0118
	Anti-C5 SoC	6/35	0.67 (0.26, 1.72)		

	Arm	n/N*	Adjusted annual rate, % (95% CI)	Rate ratio (95% CI) [†]	P value [†]
Rate of MAVEs	Iptacopan	1/62	0.03 (0.00, 0.25)	Not estimable	0.3173
	Anti-C5 SoC	0/35	0		

Iptacopan monotherapy was well tolerated and had a favorable safety profile

Most common TEAEs (≥4 patients in either arm)

n (%)	Iptacopan 200 mg bid N=62	Anti-C5 SoC N=35
Any TEAE	51 (82.3)	28 (80.0)
Mild / Moderate / Severe, %	32.3 / 45.2 / 4.8	37.1 / 34.3 / 8.6
Headache	10 (16.1)	1 (2.9)
Diarrhea	9 (14.5)	2 (5.7)
Nasopharyngitis	7 (11.3)	2 (5.7)
Nausea	6 (9.7)	1 (2.9)
COVID-19	5 (8.1)	9 (25.7)
Urinary tract infection	5 (8.1)	1 (2.9)
Arthralgia	5 (8.1)	1 (2.9)
Abdominal pain	4 (6.5)	1 (2.9)
Increased blood LDH	4 (6.5)	3 (8.6)
Dizziness	4 (6.5)	0
Breakthrough hemolysis	2 (3.2)	6 (17.1)

- **Serious TEAEs: 9.7% vs 14.3%**
- **Hemolysis serious TEAEs:**
 - **SoC:** breakthrough hemolysis (n=1) and extravascular hemolysis (n=1)
 - **Iptacopan:** None
- **No serious infections caused by encapsulated bacteria**
- **No patients discontinued study treatment, except one because of pregnancy (iptacopan)**
- **No deaths**

Conclusions

- **Oral iptacopan monotherapy** led to a significant majority of patients achieving **clinically meaningful Hb increases and Hb ≥ 12 g/dL**, associated with a higher rate of **transfusion independence** and **reduced patient-reported fatigue**, compared with SoC
- **Iptacopan monotherapy** achieved **resolution of extravascular hemolysis** and **maintenance of intravascular hemolysis control**
- Iptacopan monotherapy was well tolerated, with a **favorable safety profile** and **no serious breakthrough hemolysis**
- **Single-agent iptacopan** may represent a **practice-changing, oral, outpatient treatment for PNH patients** who have an **inadequate response** to **IV anti-C5 SoC therapy**, potentially becoming a **preferred treatment option** for patients with hemolytic PNH

Vemircopan (ALXN2050) Monotherapy in Paroxysmal Nocturnal Hemoglobinuria: Interim Data From a Phase 2 Open-Label Proof-of-Concept Study

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Masayo Ogawa,⁵ Antonio Risitano,^{6,7} Ji Yu,⁵ Jong Wook Lee⁸

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BACKGROUND ROLE OF FACTOR D

Factor D inhibitors block the complement AP and may inhibit IVH while preventing EVH

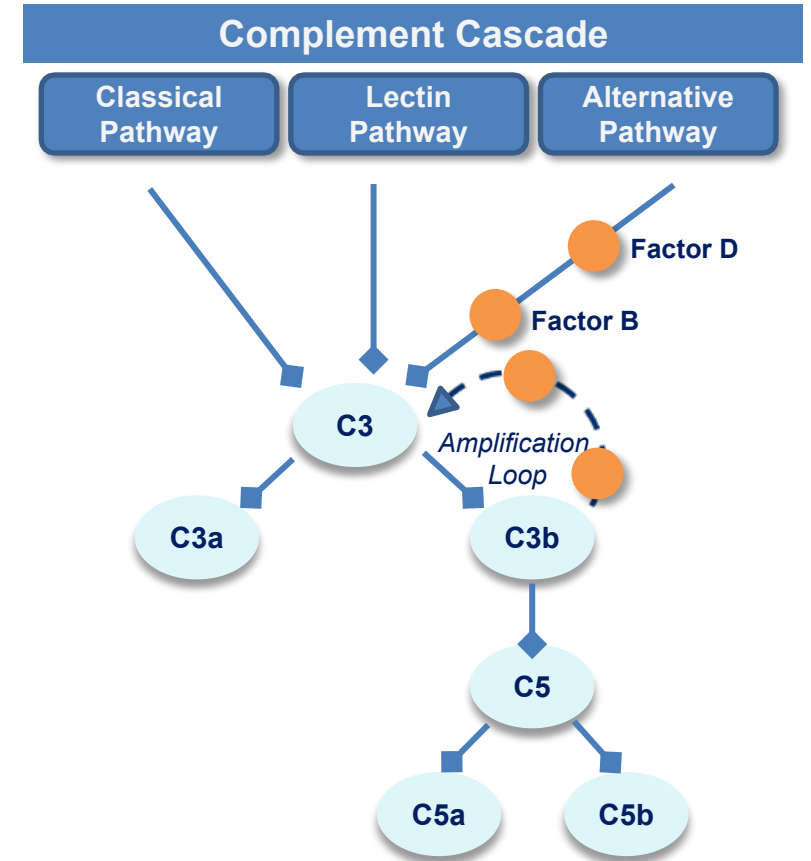
The oral factor D inhibitor danicopan (ALXN2040) showed efficacy as an add-on treatment to the C5 inhibitor eculizumab

There was unfavorable PK/PD blockade of FD in some patients when treated with danicopan as a monotherapy

Second-in-class oral Factor D inhibitor, vemircopan (ALXN2050), has the same mechanism of action as danicopan

Vemircopan demonstrates increased potency and binding affinity for Factor D and is being developed as monotherapy for PNH

Vemircopan achieves rapid, complete, and sustained AP inhibition with BID oral administration

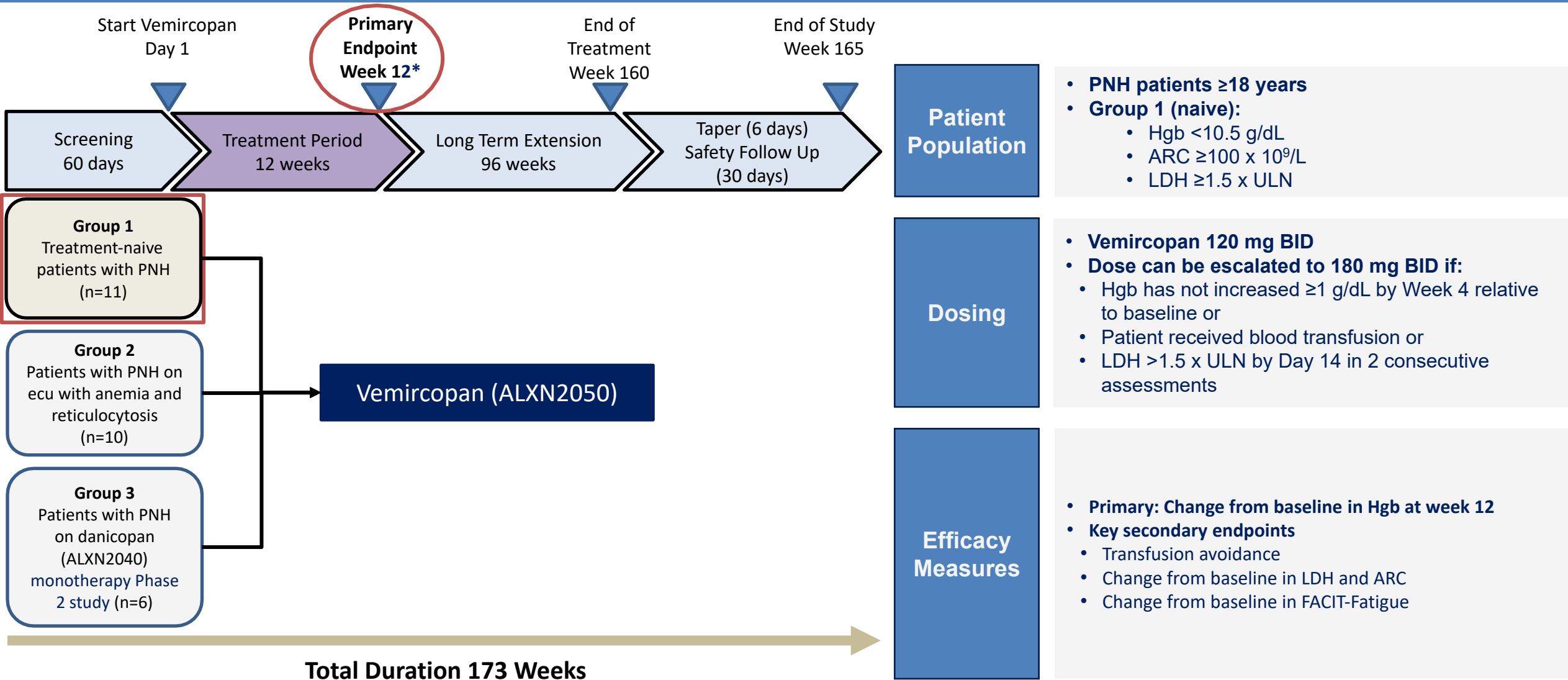


OBJECTIVE

To investigate the efficacy and safety of vemircopan monotherapy in a phase 2 study (NCT04170023) of treatment-naive adults with PNH



PHASE 2 STUDY DESIGN (NCT04170023)

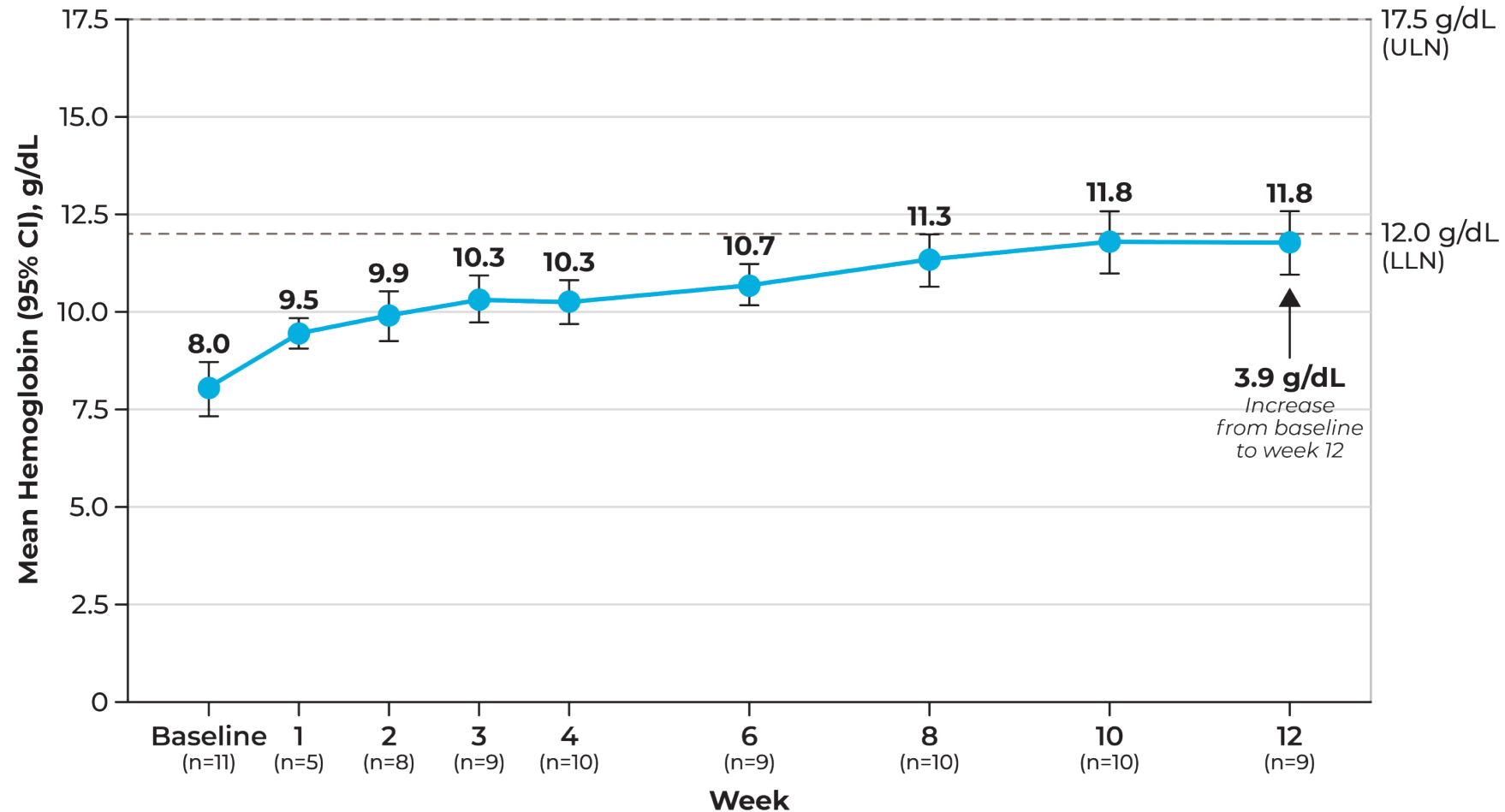


BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	Treatment-Naive Patients (n=11)
Age (years) at informed consent	
Mean (range)	44.4 (22.0–72.0)
Sex, n (%)	
Male	7 (63.6)
Female	4 (36.4)
Race, n (%)	
Asian	8 (72.7)
White	2 (18.2)
Other	1 (9.1)
Hemoglobin (g/dL)	
Mean (SD)	8.0 (1.2)
Median	8.2
Range	5.3–9.2
Lactate dehydrogenase (U/L)	
Mean (SD)	1688.0 (530.0)
Median	1743.0
Range	544.0–2358.3
Medical history	
History of aplastic anemia	1 (9.1)
History of thrombosis	0
Baseline FACIT-Fatigue Score	
Mean (SD)	30.5 (13.5)
Median	29.0
Range	10.0–49.0

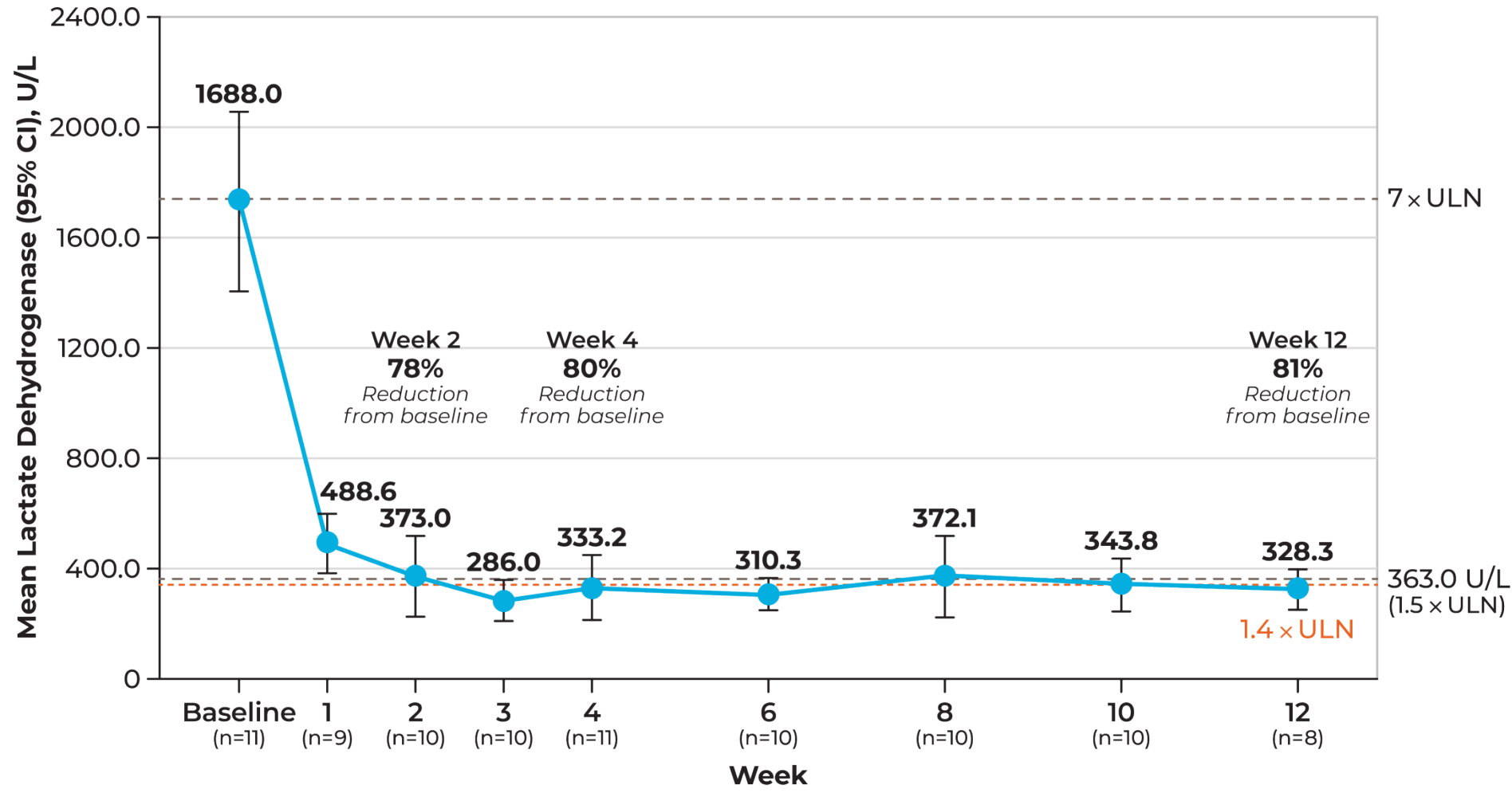


PRIMARY ENDPOINT: VEMIRCOPAN TREATMENT RESULTED IN AN INCREASE IN MEAN HEMOGLOBIN FROM BASELINE TO WEEK 12



During the 12 weeks of treatment, 8 of the 9 participants (89%) avoided blood transfusion*
In weeks 2–26, all patients avoided blood transfusion

VEMIRCOPAN TREATMENT LED TO DECREASE IN MEAN LDH FROM BASELINE TO WEEK 12



LDH reduction maintained over 12 weeks follow-up, indicating rapid and sustained control of IVH

VEMIRCOPAN IS WELL TOLERATED

	Treatment-Naive (N=11) n (%) Event (E*)
Any AE	9 (81.8) E=31
Any SAE	0
AE by relationship	
Related	4 (36.4) E=6
Not related	9 (81.8) E=25
Grade 3 or higher AEs	0
AE leading to withdrawal of study drug	0
AE leading to death	0
Common AEs (>1 patient) , n (%)	
Headache	4 (36.4)
Vomiting	2 (18.2)

- A total of 7 of the 11 participants received dose escalation from 120 mg BID to 180 mg BID
- Most AEs were mild to moderate in severity and considered unrelated to study drug
- No deaths, thrombotic events, seizures, or meningococcal infections were reported
- Hemolysis and fatigue were each reported by 1 patient (9.1%)

SUMMARY AND CONCLUSIONS

In this interim analysis of treatment-naive participants with PNH, vemircopan monotherapy controlled IVH (demonstrated by reduction in LDH to $<1.5 \times \text{ULN}$)

Vemircopan monotherapy prevented clinically significant EVH (demonstrated by 3.9 g/dL increase in Hgb level and ARC reduction) in the treatment-naive participants

Participants were less fatigued, as reflected by an improvement of 13.3 in the FACIT-Fatigue score

Vemircopan was well tolerated with no new safety signals identified during the 12-week evaluation period

This interim efficacy and safety analysis provides proof of concept for vemircopan in patients with PNH and suggests that phase 3 trials of vemircopan are warranted



PNH: Take Home Points

- **C5 inhibitors eculizumab and ravulizumab** are effective at inhibiting extravascular hemolysis in the majority of patients.
- **C3 inhibitor Pegcetacoplan** is safe and leads to long-term control of IVH and EVH.
- **Emerging therapies:**
 - In a phase 3 study, an oral proximal complement inhibitor, iptacopan, achieved clinically meaningful Hb increases and Hb ≥ 12 g/dL, associated with a higher rate of transfusion independence and reduced patient-reported fatigue, compared with SoC
 - Vemircopan monotherapy (an oral factor D inhibitor) showed efficacy in controlling with IVH and EVH in a phase 2 study (NCT04170023) of treatment-naive adults with PNH

